Movement Disorders

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Learning Objectives

- **Recognize the risk factors, signs and symptoms, and treatment of the following movement disorders: essential tremor, Huntington's Disease, and Parkinson's Disease.**

Essential Tremor

Essential Tremor-Background

- Most common movement disorder
- Incidence & prevalence varies
  - Affects ~5 million Americans
  - 1/20 people >40y/o
  - 1/5 people >65y/o
- Mean age of onset = 35 – 45 years
- Exact cause unknown

Essential Tremor-Risk Factors

- Age
  - Bimodal onset → late adolescence & older adulthood
- Males = Females
- Family history
  - 50-70% of cases are familial
  - Autosomal dominant
  - Incomplete penetrance

Essential Tremor-Genetics

- **In 1997, ETM1 gene (a.k.a. FET1) mapped to long arm of chromosome 3 @ q13**
- **2nd gene ETM2 mapped to short arm of chromosome 2 @ p22 – p25**
- **2 genes on 2 different chromosomes = multiple genes may be involved**

Essential Tremor-History

- Begins in one upper extremity; soon affects the other
- Rarely extends from UE to ipsilateral leg
- Mild degree of asymmetry is not unusual
- 30% cases involves cranial muscles
  - Head involved most frequently
  - Voice, jaw, & face follow

Essential Tremor-History (con't)

- Gradual onset
- May be intermittent initially
  - Emerges during emotional stress
  - Eventually becomes persistent
- Frequency is relatively fixed
- Amplitude varies highly depending on emotional stress

Essential Tremor-History (con't)

- **Amplitude varies highly depending on emotional stress**
  - **Worsened by emotion, hunger, fatigue, temperature extremes**
  - **Baseline amplitude slowly increases over several years**

Essential Tremor-History (con’t)

- Degree of voluntary control typical
- May be suppressed during skilled manual tasks
- Resolves during sleep or at rest

Essential Tremor-Signs/Symptoms

- Generally considered monosymptomatic, meaning tremor only
  - Few patients have abnormalities in gait & balance
  - ET diagnosis needs to be carefully reconsidered in these cases
- Tremor is postural → occurs with voluntary maintenance of position against gravity

Essential Tremor-Signs/Symptoms

- Tremor is kinetic → occurs during voluntary movement
- Tremor characteristics
  - Mild
  - Rhythmic
  - Fast
- Tone & reflexes normal

Essential Tremor-Exclusion Criteria

- Other abnormal neurologic signs, especially dystonia
- Presence of known causes of enhanced physiologic tremor (e.g., drug exposure or withdrawal)
- Sudden onset or evidence of stepwise deterioration

Essential Tremor-Exclusion Criteria

- **Isolated voice tremor**
- **Isolated position- or task-specific tremor**
- **Isolated tongue or chin tremor**
- **Isolated leg tremor**

ET vs. Parkinson's Disease

- Many associate tremor with PD
- ET & PD are not related & differ in 3 ways
  - ET occurs with activity; PD tremor occurs at rest
  - ET does not causes other health problems; PD has other health consequences
  - ET can involve hands, head, & voice; PD tremor typically only affects hands

Essential Tremor-Morbidity/Mortality

- Disability common
- 85% of patients report significant changes in livelihood & socializing
- 15% report being seriously disabled
- Decreased QOL results from loss of function & embarrassment
- Mortality rates not increased in ET patients

Essential Tremor-Treatment

- **Most patients do not need treatment beyond reassurance & lifestyle changes**
- **EtOH intake temporarily reduces tremor amplitude in 50 – 70% of cases**
- **Medications provide relief about 40 – 75% of the time**

Essential Tremor-Treatment

- **Beta Blockers**
  - **Relieve tremor in 50% of patients**
  - **Beta 2 – receptor antagonists more effective**
  - **Mechanism of action probably related to peripheral Beta 2 – receptor antagonism**

Essential Tremor-Treatment

- **Beta Blockers**
  - **Hallmark = Propranolol [generic]**
  - **Starting dose = 20mg/day & increasing by 20mg/day/week to 20mg TID**
  - **Average doses 60 – 240mg/day/TID**
  - **Some additional benefit up to 320mg/day**
- **Better choice for younger patients**

Essential Tremor-Treatment

- Antiseizure Medications
  - May be useful in patients that do not respond to Beta Blockers
  - Hallmark = Primidone [generic]
    - Starting dose = 12.5 – 25 mg/qhs
    - Increase 25 mg/week as tolerated to therapeutic level of 150 – 300 mg/qhs
    - Side effects most limiting
  - Mechanism of action unknown

Essential Tremor-Treament

- Other Medications
  - Clozapine [generic]
    - Starting dose @ 12.5mg → increase slowly
    - Long-term reduction
    - No tolerance observed
  - Mirtazapine [generic]
    - 2nd line agent
    - Helpful in ET & PD

Essential Tremor-Treament

- Other Medications
  - Gabapentin
    - Dose 400mg TID
    - Helpful when used with propranolol, but not when used alone
  - Benzodiazepines
    - Clonazepam & Alprazolam
    - Effectiveness limited, but may help reduce anxiety

Essential Tremor-Other Treatments

- **Botulinum toxin**
  - **More useful in treatment of head & voice tremor**
  - **Limited usefulness in UE tremor b/c commonly causes weakness**

Essential Tremor-Surgical Options

- Useful in severely disabling tremor not responsive to medications
- Thalamotomy
  - Destruction of brain tissue
  - Relieves tremor on other side of body
  - Not done on both sides because of increased risk of speech loss, other complications

Essential Tremor-Surgical Options

- Deep brain stimulation (DBS)
  - Thalamic stimulator device implanted into ventralis intermedius nucleus
  - May interrupt signals from thalamus that cause tremor
  - Can be performed bilaterally
  - Stimulus parameters adjusted for control
  - Foreign body in brain → risk of infection, damage to healthy tissue, etc.

Essential Tremor–Self-Care

- Avoid caffeine
- Use alcohol sparingly
- Perform special exercises
- Consider joining a support group

Huntington’s Disease

Huntington's Disease-Background

- **Progressive, fatal, neurodegenerative disorder**
- **1st described in 1872 by Dr. George Huntington ("On Chorea")**
- **Frequency = 3-7/100K (European descent)**
  - **Males = Females**
  - **Crosses all ethnic & racial boundaries**
- **>250K Americans have HD or at risk of inheriting HD**

Huntington's Disease- Background

- Mean age of onset = 35 – 42 y/o
  - Range from 1st to 8th decades
- Characterized by:
  - Motor abnormalities
  - Intellectual deterioration
  - Psychiatric symptoms
- Progression is slow
  - Lasts 10-20 years
  - Ultimately ends in death

Huntington's Disease-Genetics

- Autosomal dominant inheritance
  - 100% penetrance
- Genetic marker discovered in 1983
- Gene mutation identified in 1993

Huntington's Disease-Genetics

- **Chromosome 4; 1st exon of *HD* gene**
  - **Expansion of a C-A-G repeat region**
  - **Repeat # range in normal people = 6 – 39**
  - **Repeat # range in affected people = 36 – 180**
    - **Most between 40 – 55 repeat units**
  - **Encodes a 350-kDa protein of unknown function**

Huntington's Disease-Molecular Basis

- **C-A-G codes for glutamine**
- ***HD* protein htt has polyglutamine tract in N-terminal region**
  - **Tract size corresponds to # of C-A-G repeats**
  - **O/w size of C-A-G repeat has no effect on transcription of *HD* gene/translation of protein**

Huntington's Disease-Molecular Basis

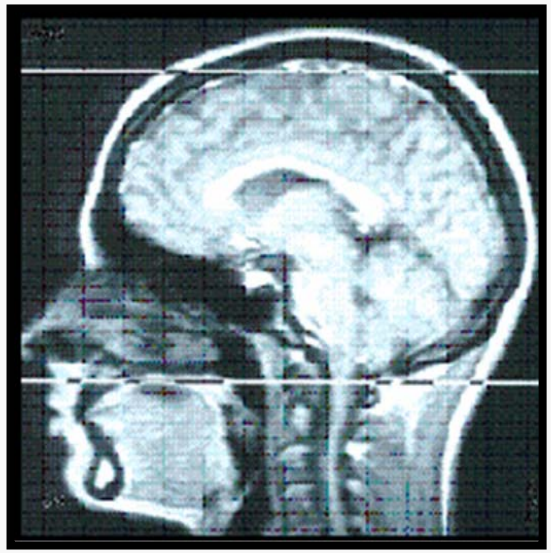
- **Expanded polyglutamine tract in htt protein plays critical role in formation of neuronal intranuclear inclusions = characteristic of HD**

Huntington's Disease-Pathology

- Results from genetically programmed degeneration of neurons
  - Mediated by excitatory amino acids
  - Released from other neurons undergoing excessive excitation → exhaustion of the neuron → death

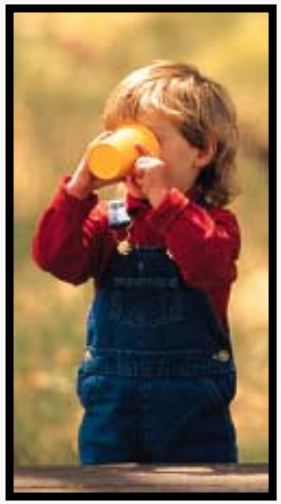
Huntington's Disease-Pathology

- **Majority of damage involves the basal ganglia**
- **Brains of HD patients weigh about 30% less than normal brains**



Juvenile HD

- A.K.A. Westphal variant or akinetic-rigid HD
- Onset before 15 y/o (as early as 2 y/o)
- Rapidly progressive
  - Mean duration = 8 – 10 years
- Hallmark = muscle rigidity (akinesia)
- Rarely live to adulthood



Huntington's Disease-Clinical Manifestations

- Within same family, symptoms vary
  - In rate of progression
  - In age of onset
- Clinical hallmark = chorea
  - Jerky, rapid, uncontrollable movement of limbs, trunk, & face
  - Does not have to be present to establish the diagnosis

Huntington's Disease-Symptoms

- Early symptoms affect cognitive ability or mobility
  - Depression, mood swings
  - Forgetfulness, clumsiness
  - Involuntary twitching
  - Lack of coordination
- Patients frequently try to "camouflage" some movements by incorporating them into semi-purposeful activities

Huntington's Disease-Symptoms

- With disease progression, symptoms include:
  - Concentration, short-term memory decrease
  - Involuntary movements increase
  - Walking/speaking/swallowing abilities decrease
- Death follows from complications of choking or aspiration, infection, poor nutrition, or heart failure

Huntington's Disease-Medical Treatment

- Education
- Depression
  - Tricyclic antidepressants
    - Amitriptyline [generic]
    - Imipramine [generic]
    - Nortriptyline [generic]
  - Serotonergic agents
    - Generics Fluoxetine, Sertraline

Huntington's Disease-Medical Treatment

- Agitation can be helped with anxiolytics
- Manic behavior
  - Carbamazepine [generic]
  - Valproate [generic]
  - Lithium [generic]
- Impulse behavior may respond to generics Clonidine or Propranolol

Huntington's Disease-Medical Treatment

- Chorea best treated with neuroleptics
  - Dopamine blocking drugs
    - May cause tardive dyskinesia
  - Monoamine depleting drugs
    - Do not cause tardive dyskinesia
  - Most effective drug: Tetrabenazine [generic]
    - Currently investigational in U.S.

Huntington's Disease-Medical Treatment

- Energy metabolism improvement → may protect against toxicity
  - Coenzyme Q10
  - Nicotinamide
- Glutamate inhibition
  - Receptor blockers
    - Remacemide [generic]
  - Inhibitors of release or synthesis: generics Riluzole, Lamotrigine, Gabapentin

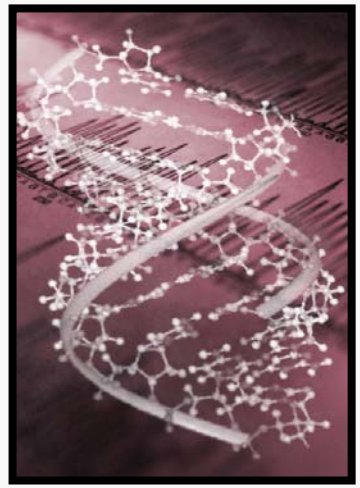
Huntington's Disease-Non-pharmacologic Treatment

- Maintain proper nutrition
  - HD patients may burn up to 5K calories/day
  - Consider extra vitamins & supplements
- Maintain proper hydration
  - HD can make patients vulnerable to dehydration

Huntington's Disease-Non-pharmacologic Treatment

- Exercise regularly
  - HD patients who exercise tend to fare better than those who do not
  - Take measures to ensure stability & prevent falls

Huntington's Disease-Genetic Testing



- Direct gene mutation detection methods are available: Sensitivity/specificity nearly 100%
- Multiple psychological issues with testing
  - ? of increased risk of suicide
    - 4X increase in suicide rate among HD patients

Huntington's Disease-Genetic Testing

- Other psychological issues with testing
  - Increased risk to children if found to be a carrier
  - Absence of a cure
  - Potential loss of health insurance
- May benefit from psychological counseling before deciding to be tested

Parkinson’s Disease

Parkinson's Disease- Background

- First described by James Parkinson in 1817
  - 6 cases
  - "The shaking palsy"
  - Cause unknown

Parkinson's Disease-Background (con't)

- 1916-1930s → epidemic of von Economo encephalitis
  - Large proportion of these patients later developed a Parkinson-like syndrome → Postencephalitic Parkinsonism (PEP)
- 1930s-1940s → PEP cases made up 1/3 – ½ of Parkinson's patients in Europe & N.A.
- 1960 → biomechanical basis identified

Parkinson’s Disease-Etiology

- **Progressive neurodegenerative disorder**
- **Cell death in the substantia nigra (SN)**
- **Decrease in brain dopamine (DA) levels**

Parkinson's Disease-Incidence

- **Increases dramatically with age**
- **Overall incidence = 20.5/100K**
- **Onset <30 y/o rare**
- **4-10% have onset before 40 y/o**
- **40-49y/o → 5/100K incidence**

Parkinson's Disease-Incidence (con't)

- In U.S.A. ~200/100K (0.2%) in 70-80s age group → 35 times higher incidence
- In other countries (Iceland, India, Scotland, Australia) 1,000-2,000/100K (1-2%)
- Mean age of onset = 60 y/o
- Most common onset in 50-79 y/o age groups

Parkinson's Disease-Prevalence & Survival

- Average = 300/100K
- Before Levodopa,
  mean survival = ~9.5 years
- After Levodopa,
  mean survival increased ~5 years
- Unidentified in many community-dwelling patients
  - Up to 42% of PD patients may be undiagnosed at any time

Parkinson's Disease-Lifetime Risk

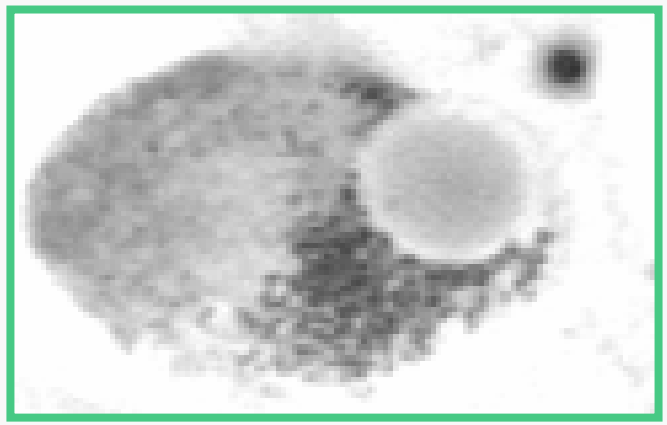
- 1950s = 2.5% (1/40 in general population)
- Today = >2.5% & may be as much as 2X that of 1950s
- Males = Females
- Black = White (in same community)

Parkinson's Disease-Pathology

- Most common site = SN pigmented neurons
- Normal → convert endogenous & exogenous Levodopa to Dopamine → striatum via nigrostriatal tract
- Abnormal → marked deficiency of DA in the striatum
  - Bradykinesia most closely correlates with degree of striatal DA deficiency

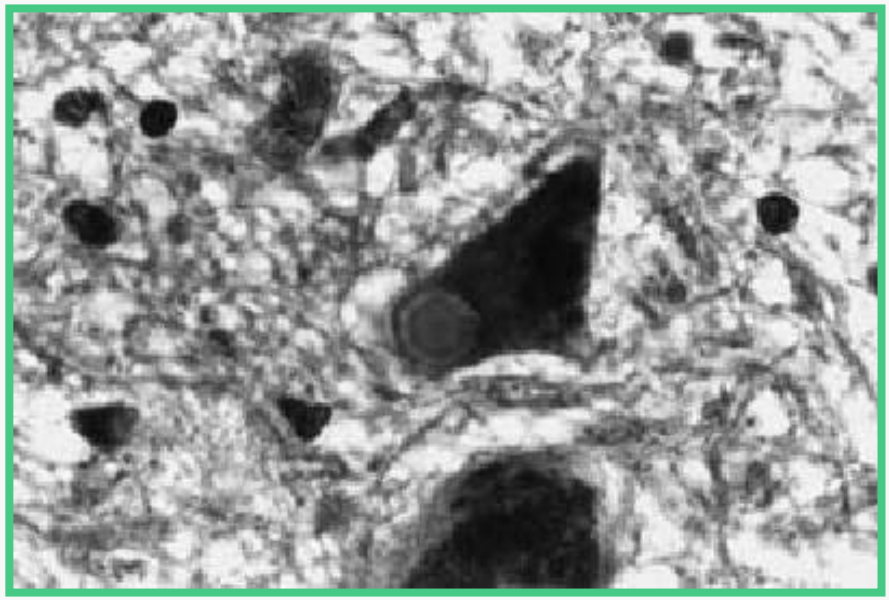
Parkinson's Disease-Pathology

- **Lewy body = intracellular inclusion body in the SN**
  - **Pathologic hallmark in Parkinson's brains**

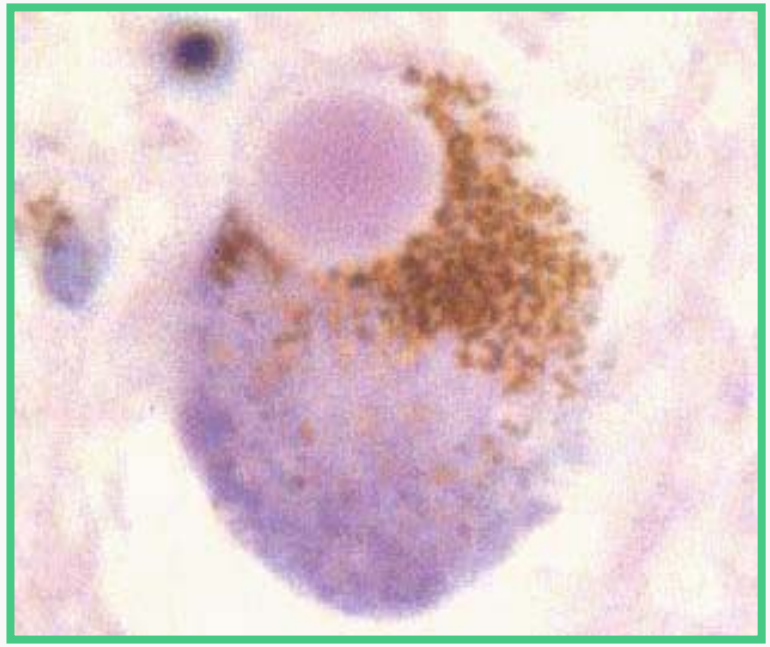


Lewy body

Lewy Bodies

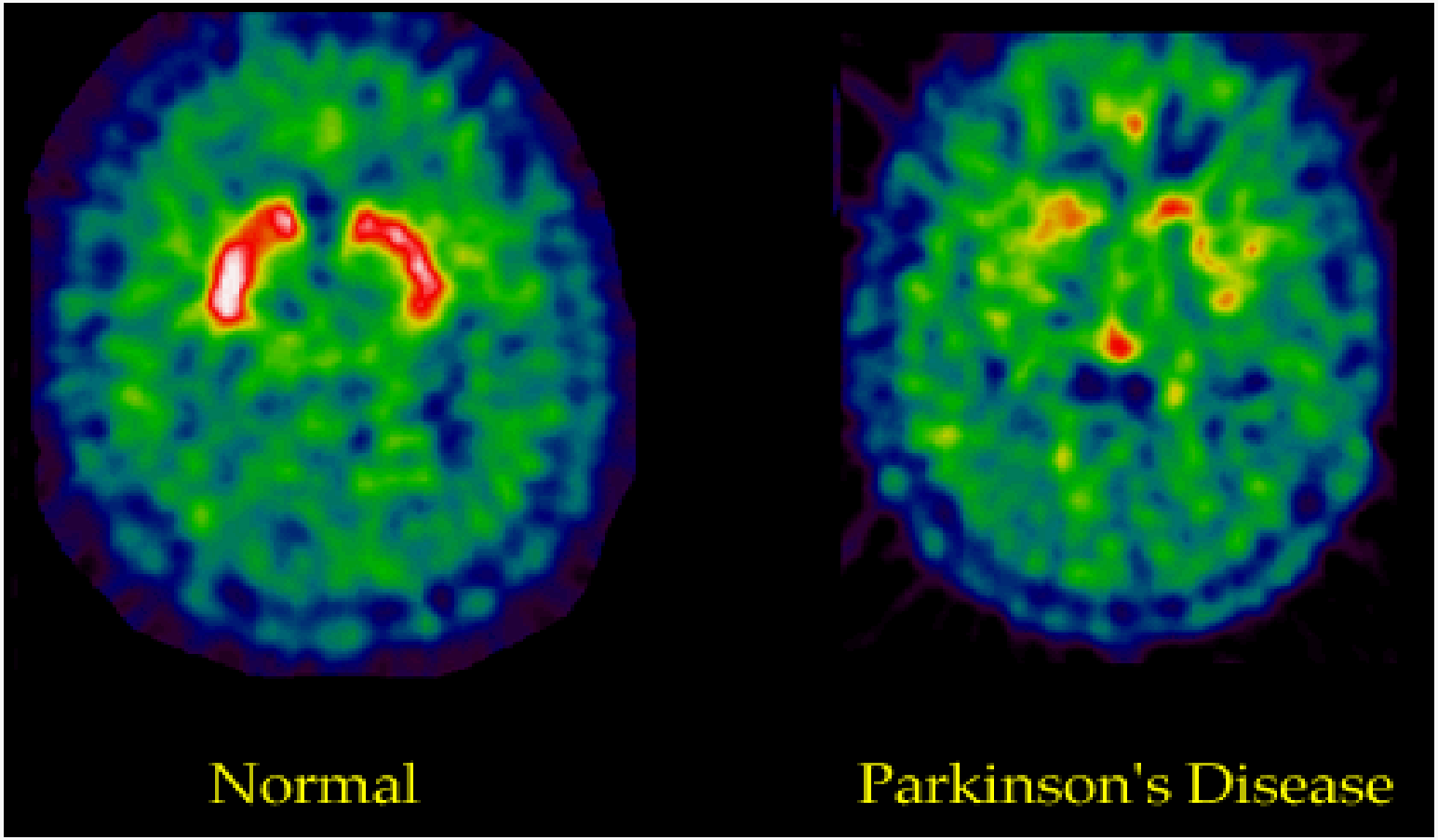


Lewy Bodies



Lewy bodies in a neuron from the substantia nigra in Parkinson’s Disease

PET Scan Images



Parkinson's Disease-Special Cases

- In small proportion of cases, PD clusters in families
- Genetic basis
- Region on long arm of Chromosome 4
- Encodes a neuronal protein alpha-synuclein
  - Role of this protein still unclear; ? association with beta-amyloid accumulation

Drug-Induced Parkinson's (DIP)

- **Any drug that depletes Dopamine storage capacity**
- **Any drug that blocks post-synaptic Dopamine receptors**
- **Produces functional striatal Dopamine deficiency**
- **Predisposition for this in the elderly 2* natural age-related SN neuronal loss & Dopamine decline**

DIP (con't)

- **Elderly patients need lower doses of Dopamine-blocking agents to produce DIP**
- **Treatment = stop the drug…**
- **May be several months before DIP resolves**
- **Important to review patient's drug history CAREFULLY**
- **More common in patients residing in chronic care institutions**

Other Causes of Parkinsonism

- Vascular (rare)
- Trauma (e.g. ?Mohammed Ali)
- Hydrocephalus (e.g. Billy Graham)
- Environmental toxins
  - Manganese
  - Pesticides
  - MPTP

Parkinson's Disease-Diagnosis

- History & clinical assessment
- No specific lab abnormalities
- Minimum requirement of 2/3 major clinical features
  - Resting tremor
  - Bradykinesia
  - Rigidity

Parkinson's Disease-Motor Symptomalogy

- Have to lose 60% of nigral neurons with 80% depletion of striatal DA before symptoms of PD develop
- Insidious onset
- Asymmetric
- First symptom = tremor
  - Usually at rest
  - Pill-rolling, one hand involved
  - Decreased with purposeful movement

Parkinson's Disease-Motor Symptomalogy (con't)

- Bradykinesia = slowness in initiating movement
- Muscular rigidity
  - Feel on passive movement of joint
  - Smooth resistance or superimposed ratchet-like jerks
    - Cogwheel rigidity
- Postural instability (late)

Parkinson's Disease-Mental Manifestations

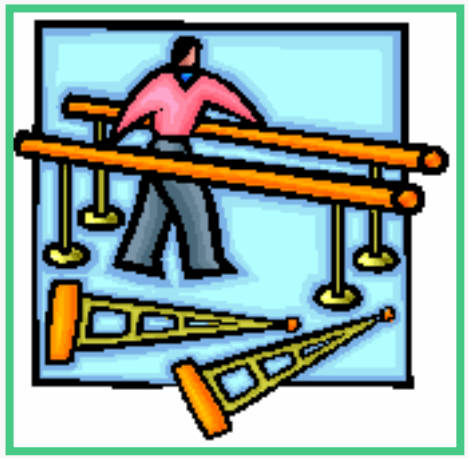
- **Depression (common)**
- **Bradyphrenia (slowed thinking)**
- **Dementia (20-25%)**

Parkinson's Disease-Treatment Goals

- Adequate symptomatic benefit
- Minimize disability
- Avoid, delay, or reduce complications/side effects of treatment
- Slow or halt progression of disease

Parkinson's Disease-Non-Pharmacologic Treatment

- Physical therapy
- Occupational therapy
- Speech therapy
- Social interaction!!!!



Anticholinergics

- Least potent in treating PD
- Effective for tremor control
- Caution when used in the elderly
- Examples:
  - Trihexyphenidyl [generic] (Artane®)
  - Benztropine [generic] (Cogentin®)
  - Ethopropazine [generic] (Parsitan®)

Sinemet® – 1st line (Levodopa/Carbidopa)

- Dopamine precursor combined with an inhibitor of peripheral Dopamine decarboxylation
- Most potent symptomatic treatment
- Start when symptoms become disabling
- Problem with sudden start/stop effect
- “Wears off” after 3-4 years of treatment

COMT Inhibitors

- **Catechol-O-methyltransferase (COMT) enzyme → breakdown of DA before it gets to the brain**
- **Adjunct to L-dopa**
- **Possible 2nd line agents**
- **Increase “on” time**
- **Decrease “off” time**

COMT Inhibitors

- Reduce L-dopa dosage
- Examples:
  - Tolcapone [generic] (Tasmar™)
  - Entacapone [generic] (Comtan®)
    - Avoid abrupt withdrawal

Selegiline [generic] (Eldepryl®)

- Monoamine oxidase B inhibitor
- Minimal symptom relief
- Adjunct to L-dopa
- Thought to be neuroprotective & prevent progression
- Delays need for L-dopa but does not delay progression

Dopamine Agonists – 2nd line

- Act on post-synaptic Dopamine receptors
- Older drugs less potent & more side effects
  - Bromocriptine [generic] (Parlodel®)
  - Pergolide [generic] (Permax®)

Dopamine Agonists – 2nd line

- Newer drugs more potent, less side effects, & slow disease progression
  - Ropinirole (Requip™)
  - Pramipexole (Mirapex®)
    - May now be 1st line agent

Amantadine [generic] (Symmetrel®)

- Mechanism of action unknown
- Hypothesis → acts as NMDA (N-methyl-D-aspartate) receptor antagonist
- Less potent than L-dopa
- Stronger than anticholinergics
- Respond initially, but quick failure (months)
- One failure does not exclude benefits forever

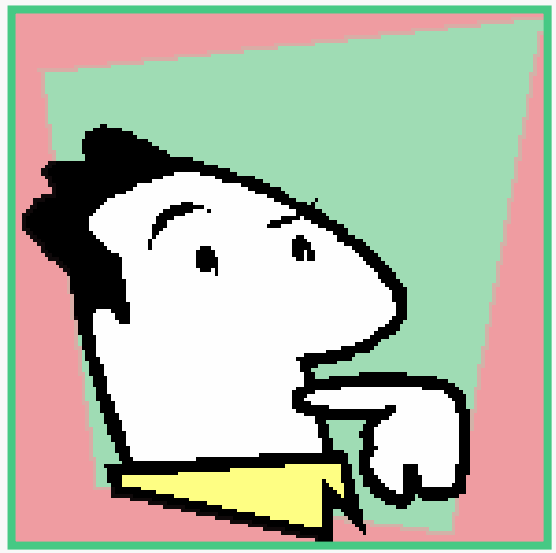
Parkinson's Disease-Surgical Options

- Ablative options
- Uni- or Bilateral thalamotomy
- Uni- or Bilateral pallidotomy
- Uni- or Bilateral subthalamotomy

- Deep Brain Stimulation
- Uni- or Bilateral of VIM
- Uni- or Bilateral of pallidus
- Uni- or Bilateral of subthalamus

Parkinson's Disease-Adverse Events with Ablative Procedures

- Dysarthria
- Dysphagia
- Cognitive changes
- Mild paresis
- Dyskinesias



Deep Brain Stimulation Advantages

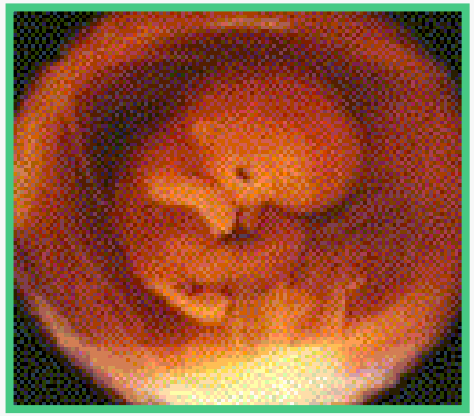
- No destruction of brain tissue
- Can adjust stimulus parameters
- Can perform bilateral operations
- Significant reduction (50-75%) in medication
- Completely reversible… patient returns to previous state if device is turned off

Deep Brain Stimulation Disadvantages

- Implanted foreign body → risk of infection
- Equipment failures occur
- Battery replacement necessary
- Possible electromagnetic interference
- Time & effort needed for programming
- Cost (~$10-$12K)

Transplantation

- **Experimental procedures**
- **Fetal tissue**
- **Genetically altered Dopamine-producing cells**
- **Glial-derived neurotrophic factor (GDNF) under investigation**

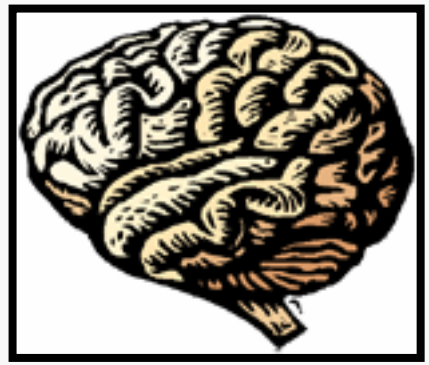


Transplantation Advantages

- **No destructive brain lesion**
- **Consistent clinical benefit & fetal Dopamine uptake**
- **Cells survive & re-innervate striatum**

Transplantation Disadvantages

- Needle passage through brain
- Optimal target still unidentified
- Limited number of centers performing these procedures
- Societal & logistic concerns
- ? Disabling dyskinesias



Summary

- **Risk factors, signs and symptoms and treatment for essential tremor, Huntington’s Disease, and Parkinson’s Disease.**